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NIDN-10375

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	A. Bjørnerud, et al.	Group Art Unit:	To be assigned
Serial Number:	09/815,140	Examiner:	To be assigned
Filing Date:	March 22, 2001		
Title:	Method of Magnetic Resonance Imaging		

COMPLETION OF CLAIM FOR PRIORITY

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicants hereby submit the official certified copy of the priority document number **GB 9821038.8** in connection with the above identified application, benefit of which is claimed in the declaration of this application. The Examiner is most respectfully requested to acknowledge receipt of this certified copy in the next Official Office Action.

Respectfully submitted,

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1.	**Your reference**	44.67996/000
		29SEP98 E393148-5 D00027 P01/7700 25.00 - 9821038.8
2.	**Patent application number** *(The Patent Office will fill in this part)*	**9821038.8**
3.	**Full name, address and postcode of the or of each applicant** *(underline all surnames)*	Nycomed Imaging AS Nycoveien 1-2 N-0401 Oslo Norway
	Patents ADP number *(if you know it)*	62891280001
	If the applicant is a corporate body, give country/state of incorporation	Norway
4.	**Title of the invention**	Method
5.	**Name of your agent** *(if you have one)*	Frank B. Dehn & Co. Anthony Rollins John Hamer Caterina MacLeod NYCOMED AMERSHAM PLC AMERSHAM LABORATORIES WHITE LION ROAD AMERSHAM, BUCKS.
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	179 Queen Victoria Street London EC4V 4EL
	Patents ADP number *(if you know it)*	166001
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7.	**If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application**	**Number of earlier application** / **Date of filing** *(day / month / year)*
8.	**Is a statement of inventorship and of right to grant of a patent required in support of this request?** *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *See note (d))*	Yes

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11. **I/We request the grant of a patent on the basis of this application.**

Signature **Date** 28 September 1998

Frank B Dehn & Co

12. Name and daytime telephone number of person to contact in the United Kingdom

Julian Cockbain
0171 206 0600

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Method

This invention relates to improvements in and relating to methods of magnetic resonance imaging, in particular imaging of blood oxygenation levels, and to the use of magnetic materials for the manufacture of contrast media for use in methods of diagnosis involving such methods of imaging.

In magnetic resonance angiography, magnetic resonance (mr) imaging of the vascular tree, it is a problem to distinguish arteries from veins. Conventional mr contrast agents with a prolonged blood half life, ie. which remain in the circulating blood for a prolonged period, will generally give equal enhancement of veins and arteries. Consequently, in the resultant mr images, arteries cannot be distinguished from veins.

The present invention relies on the use of a contrast agent which has a water proton T_2 and T_1 reducing effect and which is retained in the blood plasma, i.e. which neither distributes significantly into the interstitium nor crosses cell membranes. With such contrast agents, hereinafter referred to as "T_2 blood pool agents", present in the blood there are two different contributions to T_2 reduction for water protons in blood - reduction due to diffusion past the contrast agent in the blood and reduction due to diffusion through the magnetic field gradients due to the differences in magnetization between the interior and exterior of the red blood cells. The second of these contributions is dependent on the oxygenation state of the haemoglobin in the red blood cells. In the veins the haemoglobin is deoxygenated and as a result the red blood cells are paramagnetic while in the arteries the haemoglobin is oxygenated and the red blood cells are diamagnetic. Thus the differences in magnetization

between the interior of the red blood cells and the exterior contrast agent containing plasma are lower in the veins than in the arteries and T_2 will accordingly be larger. Since the magnetization difference contributes only to a T_2 reduction and not a T_1 reduction, the mr signal intensity from the veins will be greater than from the arteries.

A further effect also facilitates differential enhancement of the venous signal relative to the arterial signal. Thus since blood flow is generally slower and less pulsatile in veins, there is less signal loss due to intravoxel dephasing in veins than in arteries.

While the contrast agent is referred to as a T_2 blood pool contrast agent, this is not intended to indicate that the T_2 reducing effect of the contrast agent dominates over its T_1 reducing effect in terms of its overall effect on mr signal intensity. Thus the T_1 reducing effect may indeed dominate in veins and even in arteries with the result being an increase in mr signal strength. In other words the T_2 blood pool contrast agent may nonetheless function as a "positive" contrast agent, that is to say one which increases mr signal strength in the regions into which it distributes.

Thus viewed from one aspect the present invention provides a method of magnetic resonance imaging of regional blood oxygenation which comprises administering into the vasculature of a vascularized human or non-human animal (e.g. a mammal, reptile or bird) subject a T_2 blood pool contrast agent, detecting a magnetic resonance signal from at least part of the vasculature of said subject into which said contrast agent distributes, and manipulating said signal to generate an image indicative of the partial pressure of oxygen (pO_2) in at least part of said vasculature, e.g. to differentiate between veins and arteries or to identify a region of ischemia.

Viewed from another aspect the invention provides a method of magnetic resonance imaging of regional blood oxygenation which comprises administering into the vasculature of a vascularized human or non-human animal subject a T_2 blood pool contrast agent, detecting a magnetic resonance signal from at least part of the vasculature of said subject into which said contrast agent distributes, and manipulating said signal to provide differential enhancement of arteries and veins.

Since the magnetization of the blood plasma, following administration of the T_2 contrast agent into the vasculature, is dependent on the local concentration and the magnetization of the contrast agent, the difference in mr signal intensity between arteries and veins or between normal and ischemic tissue will be dose-dependent and also, in echo imaging techniques, echo time (TE) dependent. Thus, in one preferred embodiment of the invention, mr signal detection and manipulation will involve generation of (at least) two mr images, one more T_2 dependent than the other, and comparison of the images whereby to selectively visualize regions of lower or higher blood oxygenation. Such comparison may for example involve subtraction of one image from the other, optionally after normalization of one or both images to enhance the selective visualization, e.g. by setting the image intensity for a selected region of interest to the same value in both images.

The relatively more and less T_2 dependent images may be generated by conventional mr imaging sequences, e.g. from echo sequences involving shorter or longer echo times generated sequentially or alternatingly (i.e. interleaved sequences). In a particularly preferred embodiment however a double echo sequence may be used with the two images being generated from earlier and later echos. Thus a double echo sequence may advantageously be used - the first (short TE) echo will

give almost equal signal intensity for veins and arteries (or normal and ischemic tissue) while the second (long TE) echo will have higher signal intensity for veins than for arteries, etc. Subtracting the first image from the second will selectively visualize arteries or veins. Furthermore by evaluating the relative degree of oxygenation (i.e. pO_2) of the blood flowing to and from a tissue or organ, the oxygen consumption of that tissue or organ can be evaluated. The blood pO_2 can be determined in a quantitative, semi-quantitative or qualitative manner, for example by comparison with calibration values determined for known pO_2 and contrast agent concentration values.

Thus viewed from a further aspect the invention provides method of magnetic resonance imaging of a human or non-human animal subject which comprises administering into the vasculature of said subject a T_2 blood pool contrast agent, generating at least two images of at least part of said subject, a first of said images being more T_2-dependent than a second of said images, and comparing said first and second images (e.g. by subtraction of one from the other) whereby to obtain an image providing an indication of regional blood oxygenation in said subject.

In the methods of the invention, the contrast agent dosage will preferably be such as to substantially cancel out the magnetization difference between plasma and deoxygenated (venous) blood. The appropriate dosage will thus depend on the blood pool volume of the subject, the red blood cell count of the subject, the magnetic susceptibility of the contrast agent and the field strength of the magnet in the mr imaging apparatus. The first of these can readily be estimated to a sufficient level of accuracy, the second can be measured or estimated, the third can readily be measured and the fourth is known for each apparatus.

It is known that the susceptibility difference $\Delta\chi$

between red blood cells and plasma in venous blood with about 50% hematocrit is about $8x10^{-8}$ cgs/cm^3. At a magnetic field strength of 1.5T this corresponds to a magnetization difference ΔM of 1.2 A/m. The magnetization at 1.5T of the PEGylated superparamagnetic particulate contrast agent described in WO97/25073 is 4.5 A/m /mMFe and as a result a dose of that agent which provides a plasma concentration of 0.26 mMFe will reduce ΔM to about zero and minimize R_2 in the venous blood. Provided that the blood iron concentration is equal to or higher than the concentration which minimizes R_2^* ($1/T_2^*$) relaxation rate of venous blood, the blood in the veins will have a greater T_2 value than that in the arteries and will thus give a greater mr signal intensity. The optimal blood iron concentration for distinguishing between venous and arterial blood will depend on the actual T_2 and T_1 values of such blood and on the mr imaging sequences used.

Generally speaking for subjects of a given species, the R_2^* values for oxygenated and deoxygenated blood may be measured at the field strength of the primary magnet of the mr imager to be used and a blood contrast agent concentration should be used at which the two R_2^* values are sufficiently different that a difference in signal intensity between venous and arterial blood may be observed (cf. Examples 3 and 4 below and Figures 2 and 3).

Approximating the blood pool volume as 80 mL/kg bodyweight for mammals such as humans this corresponds to a dosage of about 1mg Fe/kg. Thus for human subjects the contrast agent dosage will preferably be in the range 0.2 to 8 mgFe/kg bodyweight, more preferably 0.5 to 6 mg/kg, still more preferably 1 to 5 mg/kg.

Thus viewed from a further aspect the invention provides a method of magnetic resonance imaging of a mammalian, preferably human, subject which comprises administering a T_2 blood pool contrast agent into the

vasculature of said subject and generating a T_2-dependent (e.g. T_2 weighted) magnetic resonance imaging of at least part of said subject, the improvement comprising administering said contrast agent at a dosage in the range 0.2 to 8 mgFe/kg bodyweight, preferably 1 to 5 mg/kg, etc.

The methods of imaging of the invention may optionally be defined as involving only the steps subsequent to the administration of the contrast agent. Besides distinguishing between venous and arterial blood or between normal and ischemic tissue, the methods of the invention will allow lung function to be studied. Likewise the methods may be used to study kidney structure and function and tumor structure and development. Images where the contrast agent provides contrast enhancement of blood vessels may be used to detect the regions of the lung with abnormal blood supply; however the T_2 enhancement of the signals from deoxygenated blood may also be used to detect regions within the lung where oxygen uptake is abnormal, e.g. as a result of tumors or airway obstructions.

Thus viewed from a further aspect the invention provides a method of magnetic resonance imaging of lung function in a human or non-human subject, said method comprising administering into the vasculature of said subject a T_2 blood pool contrast agent, generating a T_2-dependent magnetic resonance image of at least part of the lungs of said subject and identifying regions of abnormal mr signal intensity within the lungs.

The T_2 blood pool contrast agent used in the methods of the invention may be any physiologically tolerable paramagnetic, superparamagnetic, ferromagnetic or ferrimagnetic material which may selectively increase magnetization of blood plasma without substantially influencing the pO_2 within the red blood cells. Conveniently the material will be one which has a blood half life (measured for example in the pig) of at least

30 minutes, preferably at least 1 hour. Generally the contrast agent will be a water-soluble or water-dispersible material, e.g. a polychelate (preferably a dendrimeric polychelate) of a transition metal or lanthanide or it will be a particulate material, e.g. having a particle size of 1 to 8000nm, preferably 5 to 500nm, especially preferably a particulate material having on or as its surface a blood residence prolonging agent, for example a polyalkylene oxide (e.g. polyethyleneglycol) or a glycosaminoglycan (e.g. heparin, dermatan, hyaluronic acid, keratan, chondroitin, etc.). Particulate agents may be solids (e.g. single substances or aggregates containing a matrix material and a magnetic material) or they may even be droplets of water-insoluble liquid materials. Particulate agents will generally be preferred to water soluble agents.

The magnetic property of the contrast agent which is of particular concern is its magnetic susceptibility. Accordingly where the contrast agent is paramagnetic it is preferred that the paramagnetic centres be high susceptibility lanthanide metal ions which possess high T_1 relaxivity, such as for example Gd or Eu. The magnetic susceptibility of superparamagnetic materials is markedly higher than that of paramagnetic materials and it is especially preferred that the T_2 contrast agent be or contain a superparamagnetic material, e.g. an iron oxide or mixed iron oxide, for example magnetite.

Many susceptibility agents have been described in the patent literature by companies such as Nycomed, Schering, Advanced Magnetics, Silica Gel, BASF, Sterling Winthrop, MBI, The General Hospital Corp, Meito Sangyo, etc. An exemplary T_2 blood pool agent is the PEGylated superparamagnetic material disclosed by Nycomed Imaging AS in WO97/25073.

Thus viewed from a further aspect the invention provides use of a physiologically tolerable

paramagnetic, ferrimagnetic, ferromagnetic or more preferably superparamagnetic material for the manufacture of a contrast medium for use in a method of diagnosis which involves a method of imaging according to the invention.

The invention will now be described further with reference to the following non-limiting Examples and the accompanying drawings in which:

Figure 1 is a plot of T_2^* (for water protons) as a function of contrast agent concentration in venous blood;

Figure 2 is a magnetic resonance image of the human groin produced using a method according to the invention;

Figure 3 is a plot of R_2^* (ie. $1/T_2^*$) values against iron concentration obtained at 300 MHz in fully oxygenated (▲) and fully deoxygenated (♦) blood;

Figure 4 shows a plot of R2 relaxation rate of oxygenated and deoxygenated whole human blood as function of contrast agent concentration at 1.5 Tesla (R2 calculated using a double echo gradient echo sequence with TE1=1.7 ms and TE2=10 ms);

Figure 5 is a phantom image showing effect of oxygenation on blood signal with a 0.5 mM Fe dose of the contrast agent of Example 1 (Sample 1 contains fully deoxygenated blood with a hematocrit of 53%, Sample 2 contains fully oxygenated blood with the same hematocrit, Sample 3 contains fully deoxygenated blood with hematocrit of 23%, Sample 4 contains fully oxygenated blood with hematocrit 23% and Sample 5 contains plasma (zero hematocrit): Image sequence: 3D gradient echo, TR=10 ms, TE=6 ms, flip = 40 deg); and

Figure 6 is a difference image obtained by subtracting the first echo image (TE=1.7 ms) from the second echo image (TE=6 ms Figure 5).

EXAMPLE 1

Contrast agent

A PEGylated superparamagnetic particulate contrast agent was produced essentially as described in the Examples of WO97/25073.

EXAMPLE 2

Effect of contrast agent concentration

T_2* was determined in a field of 1.5T for samples of pig venous blood containing various concentrations of the contrast agent of Example 1. As may be seen from Figure 1, T_2* initially increases and subsequently decreases as the contrast agent concentration is increased. Maximum T_2* values occur in the concentration range 2 to 10 μg Fe/mL.

EXAMPLE 3

Imaging

A dose of 4 mgFe/kg of the contrast agent of Example 1 was administered iv to a 80 kg healthy human volunteer.

30 minutes after contrast agent administration the groin area of the volunteer was imaged in a Philips Gyroscan NT 1.5T mr apparatus using a T1-FFE imaging sequence with RT = 10 ms and TE = 4 ms. The vena cava and iliac veins were clearly visualisable whereas the arterial vessel tree had a much lower signal intensity (see Figure 2).

EXAMPLE 4

Effect of iron concentration

R_2^* relaxivity (in s^{-1}) was determined at 300 MHz (7T) using the contrast agent of Example 1 in fully oxygenated and fully deoxygenated human blood. The results are plotted in Figure 3. In oxygenated blood, R_2^* increases constantly with increasing iron concentration. In deoxygenated blood on the other hand

R_2^* initially decreases with increasing iron concentration, reaching a minimum at about 2 mMFe, whereafter it begins to increase. At all iron concentrations above 1 mMFe, R_2^* is higher for oxygenated blood than for deoxygenated blood.

EXAMPLE 5

Effect of contrast agent on fully oxygenated and fully deoxygenated blood

The effect of the contrast agent of Example 1 on fully oxygenated and fully deoxygenated whole human blood was investigated in a phantom model at 1.5 Tesla (Philips NT, Philips Medical Systems, The Netherlands). Human whole blood was obtained from a blood bank (Oslo, Norway). All blood contained 5000 TE of sodium heparin (equivalent to 1.35 ml heparin/450 ml blood) as the anti-coagulant. All blood was obtained fresh from the blood bank and stored at 4°C prior to use. All samples were analysed within 72 hours after blood collection.

Blood deoxygenation was achieved by adding sodium dithionite to the blood sample immediately prior to imaging. Fully oxygenated blood was obtained by gently bubbling oxygen through the sample.

A double echo 3D gradient echo sequence was used to calculate the R2 relaxation rate of the blood samples. The sequence parameters were as follows: TR = 13 ms, flip = 40 degrees, TE_1 = 1.7 ms, TE_2 = 10 ms, slice thickness = 2 mm, matrix = 256*256, field of view = 250 mm.

R2 relaxation rates was calculated from the signal intensity difference between the images obtained at the first and the second echo. Assuming a monoexponential decay of the signal intensity as a function of R2 relaxation rate, R2 can be expressed as follows:

$$R2\,(s^{-1}) = \ln(SI_1/SI_2)/(TE_2 - TE_1)$$

where SI_1 = Signal intensity at first echo (TE_1 = 1.7 ms)
SI_2 = Signal intensity at second echo (TE_1 = 10 ms)

Figure 4 shows the variation in R2 as a function of contrast agent concentration for fully oxygenated and fully deoxygenated blood. At the lowest concentration investigated (0.1 mM Fe), deoxygenated blood has slightly larger R2 than oxygenated blood. At higher concentrations, the R2 of oxygenated blood increased more rapidly than for deoxygenated blood. At the highest contrast agent concentration investigated (0.5 mM Fe) the difference in R2 between oxygenated and deoxygenated blood was found to be approximately 100 s^{-1}. This difference could easily be observed in the image as seen in Figure 5. The dramatic effect of changing the blood hematocrit was also notable. Sample 1 and sample 3 are both fully deoxygenated with the same contrast agent concentration. However sample 1 has a hematocrit of 53% and sample 3 has hematocrit of 23%. By subtracting the first echo from the second echo image the resulting subtraction image (Figure 6) shows more signal from the oxyogenated blood than from the deoxygenated blood because of a larger signal drop from the first to the second echo in the oxygenated blood.

Claims:

1. A method of magnetic resonance imaging of regional blood oxygenation which comprises administering into the vasculature of a vascularized human or non-human animal subject a T_2 blood pool contrast agent, detecting a magnetic resonance signal from at least part of the vasculature of said subject into which said contrast agent distributes, and manipulating said signal to generate an image indicative of the partial pressure of oxygen (pO_2) in at least part of said vasculature.

2. A method of magnetic resonance imaging of a human or non-human animal subject which comprises administering into the vasculature of said subject a T_2 blood pool contrast agent, generating at least two images of at least part of said subject, a first of said images being more T_2-dependent than a second of said images, and comparing said first and second images whereby to obtain an image providing an indication of regional blood oxygenation in said subject.

3. A method of magnetic resonance imaging of a mammalian subject which comprises administering a T_2 blood pool contrast agent into the vasculature of said subject and generating a T_2-dependent (e.g. T_2 weighted) magnetic resonance imaging of at least part of said subject, the improvement comprising administering said contrast agent at a dosage in the range 0.2 to 8 mgFe/kg bodyweight.

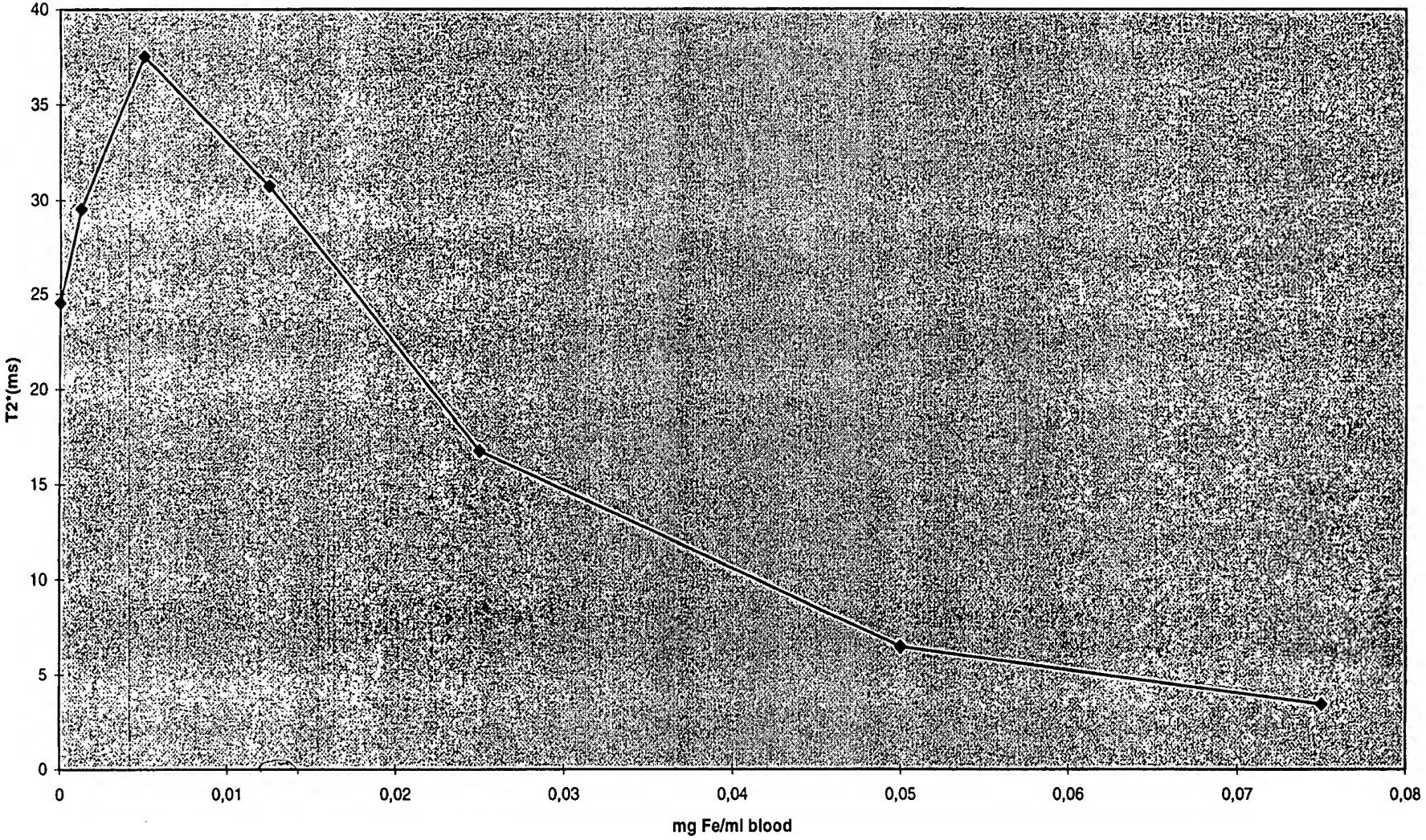
4. A method of magnetic resonance imaging of lung function in a human or non-human subject, said method comprising administering into the vasculature of said subject a T_2 blood pool contrast agent, generating a T_2-dependent magnetic resonance image of at least part of the lungs of said subject and identifying regions of

abnormal mr signal intensity within the lungs.

5. A method of magnetic resonance imaging of regional blood oxygenation which comprises administering into the vasculature of a vascularized human or non-human animal subject a T_2 blood pool contrast agent, detecting a magnetic resonance signal from at least part of the vasculature of said subject into which said contrast agent distributes, and manipulating said signal to provide differential enhancement of arteries and veins.

6. The use of a physiologically tolerable paramagnetic, ferrimagnetic, ferromagnetic or more preferably superparamagnetic material for the manufacture of a contrast medium for use in a method of diagnosis which involves a method of imaging according to any one of claims 1 to 5.

FIGURE 1


T2* as a function of concentration in venous blood
T2*(ms)
40
35
30
25
20
15
10
5
0
0
0,01
0,02
0,03
0,04
0,05
0,06
0,07
0,08
mg Fe/ml blood

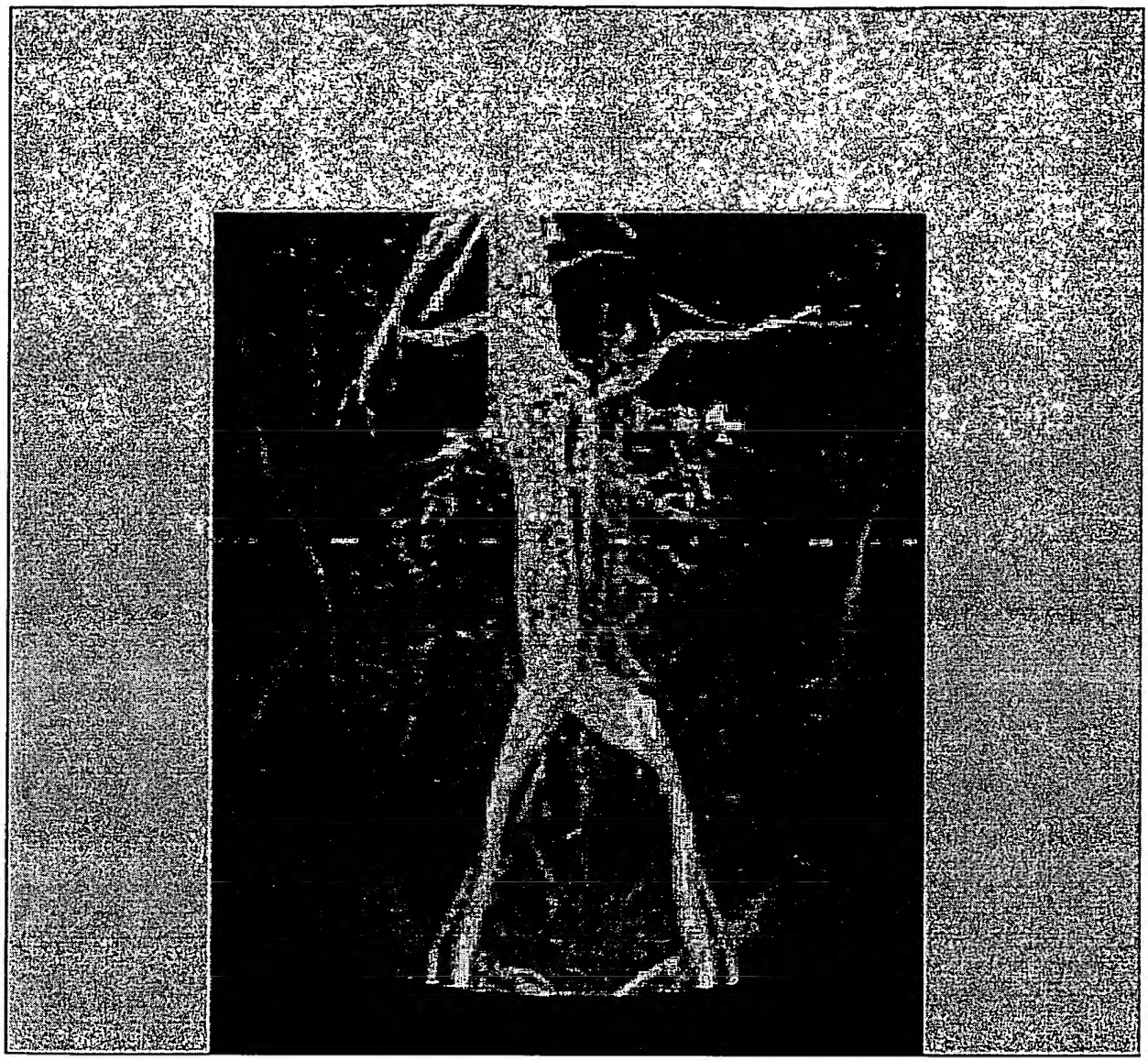


FIGURE 2

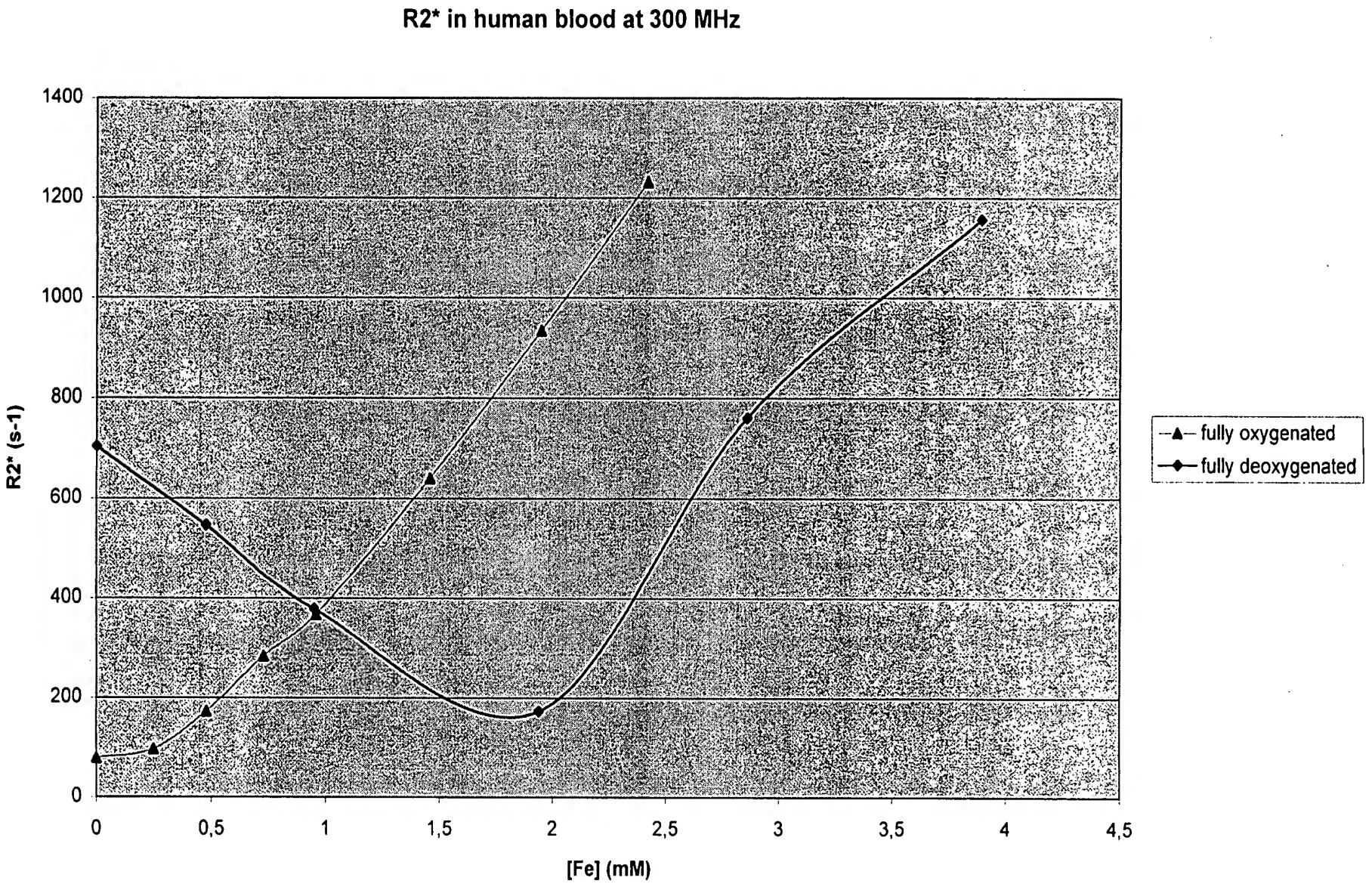

R2* in human blood at 300 MHz
R2* (s-1)
1400
1200
1000
800
600
400
200
0
0
0,5
1
1,5
2
2,5
3
3,5
4
4,5
[Fe] (mM)
fully oxygenated
fully deoxygenated

Figure 3

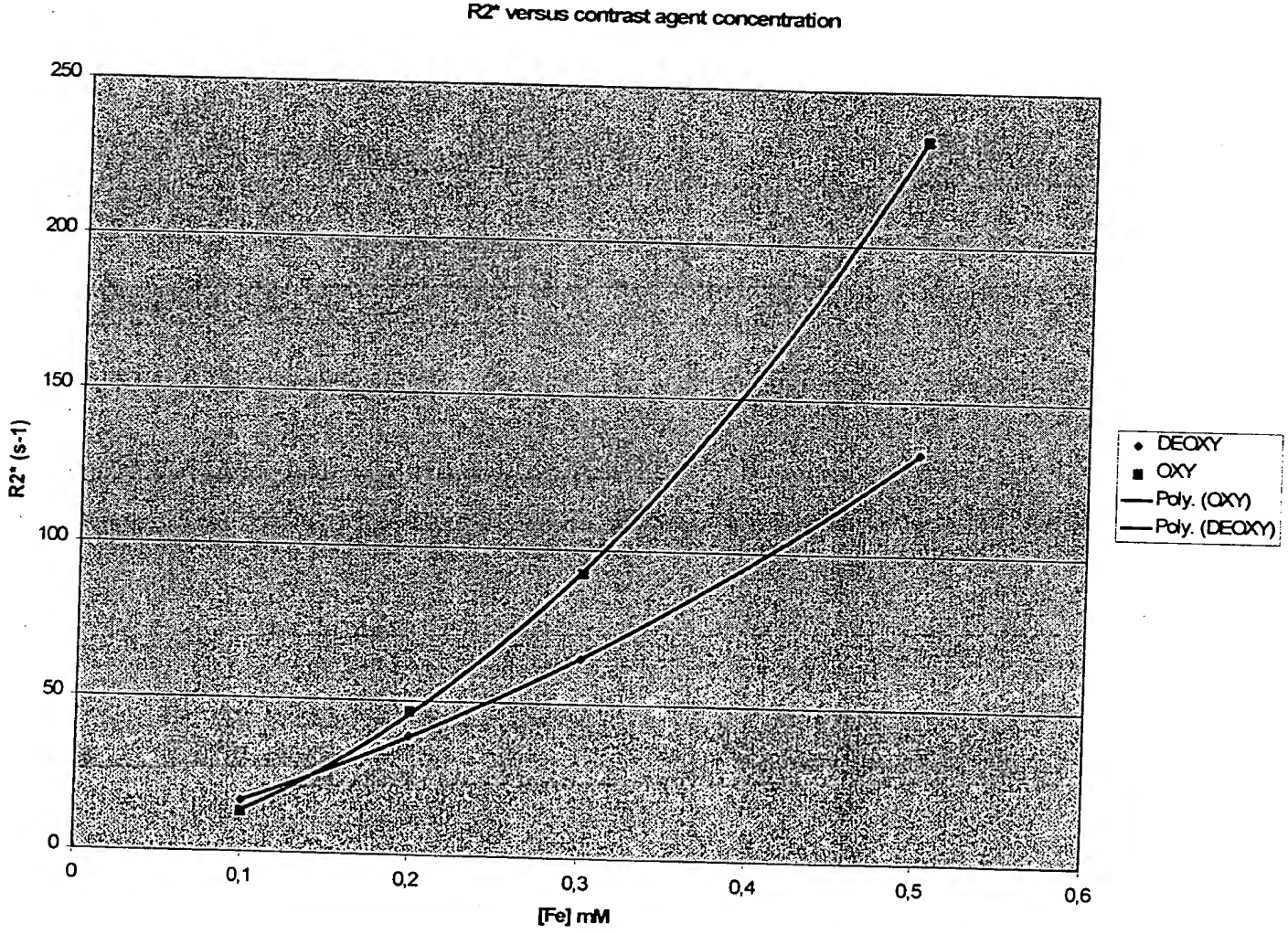

R2* versus contrast agent concentration
250
200
150
100
50
0
R2* (s-1)
0
0,1
0,2
0,3
0,4
0,5
0,6
[Fe] mM
DEOXY
OXY
Poly. (OXY)
Poly. (DEOXY)

FIGURE 4

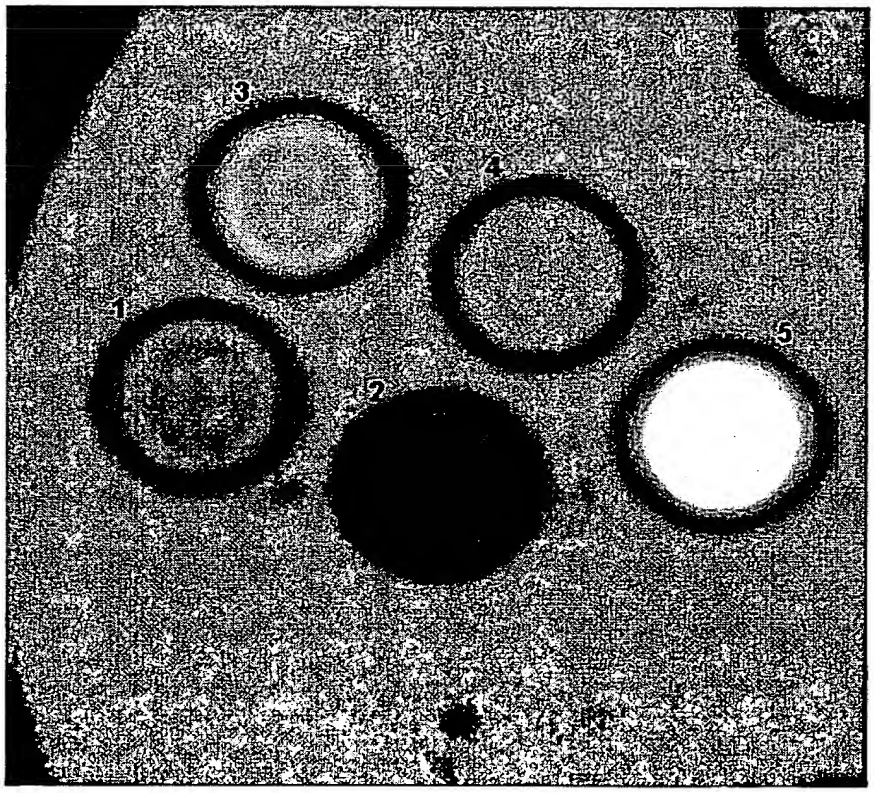


FIGURE 5

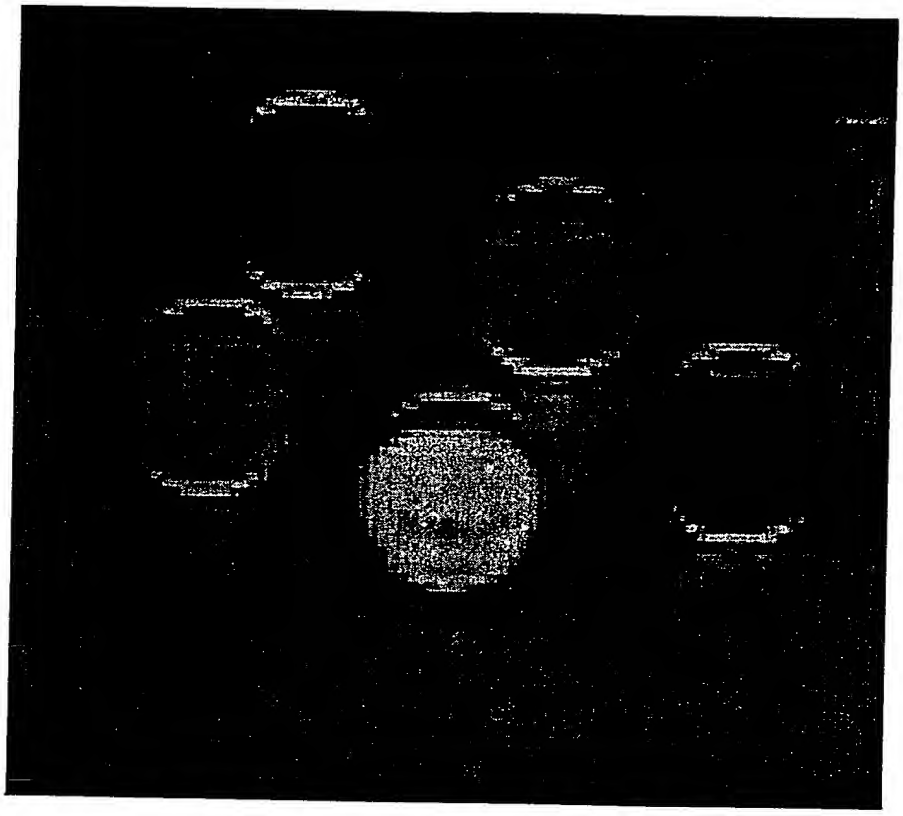


FIGURE 6